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Chapter 13

Early warning indicators for population based monitoring of HIV drug resistance in 6 African countries

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ABSTRACT

Human immunodeficiency virus (HIV) RNA testing and HIV drug resistance (HIVDR) testing are not routinely available for therapeutic monitoring of patients receiving antiretroviral therapy (ART) in resource-limited settings. World Health Organization HIVDR early warning indicators (EWIs) assess ART site factors known to favor the emergence of HIVDR. HIV drug resistance EWI monitoring was performed within the PharmAccess African Studies to Evaluate Resistance Monitoring (PASER-M) study, comprising 13 ART sites in 6 African countries. Early warning indicator assessment in the PASER network identified vulnerable aspects of ART programs and triggered interventions aimed at minimizing HIVDR emergence. Additionally, data suggest an advantage of medication possession ratio over on-time antiretroviral drug pickup in identifying patients at risk for HIVDR development.

INTRODUCTION

Major challenges to expanded access of antiretroviral therapy (ART) for human immunodeficiency virus (HIV)–infected individuals in sub-Saharan Africa arise from a deficient, under-resourced health infrastructure. Suboptimal delivery of HIV care and treatment may accelerate the emergence of drug-resistant viruses, which could impair the sustained response to first-line ART and increase the subsequent spread to newly infected individuals [1, 2]. Because HIV drug resistance (HIVDR) testing is not routinely available in resource-limited settings, the World Health Organization (WHO), as part of its global strategy for prevention and assessment of HIVDR, recommends that ART program factors, such as prescribing practices, patient retention, and drug supply and adherence, are monitored to optimize the quality of patient care [3]. World Health Organization HIVDR early warning indicators (EWIs) make use of data that are routinely collected in patients' medical and pharmacy records [4], and feasibility of their implementation has been successfully demonstrated in sub-Saharan Africa [5, 6]. However, a formal evaluation of the EWIs for their ability to identify possible HIVDR has not been performed.

Imperfect adherence to antiretroviral (ARV) medication is associated with poor virological response [7-10] and selection of drug-resistant virus [11, 12]. Patient adherence can be approximated using pharmacy pickup information, and studies have shown that drug pickup data may be considered an alternative to CD4 cell counts in predicting virological failure [13, 14]. Another adherence measure, the medication possession ratio (MPR), defined as the amount of time an individual is in possession of ARVs divided by the time between ARV prescriptions [15], has also been shown to be associated with treatment outcomes in resource-limited settings [7, 13, 16-18].

We report the results of EWI assessment in a clinical network of 13 ART sites in 6 African countries. Additionally, we sought to evaluate the EWI on-time ARV drug pickup and the MPR as measures to determine possible HIVDR after 12 months of ART.

METHODS

Study population and design

Early warning indicators were collected as part of the PharmAccess African Studies to Evaluate Resistance Monitoring (PASER-M) study, a multicenter, prospective, observational cohort of HIV-infected adults who receive first- and second-line ART under routine circumstances at 13 clinical sites in 6 African countries (Kenya, Nigeria, South Africa, Uganda, Zambia, and Zimbabwe). The sites collaborating on the PASER-M study

comprise 6 public institutions, 3 non-governmental organizations, 2 private for-profit clinics, and 2 faith-based hospitals. Cohort and site characteristics have been previously described [19]. Exclusion criteria were pregnancy at study screening and reinitiation of first-line ART < 30 days after stopping previous ART. Any other prior ARV drug use was not an exclusion criterion. Participants were consecutively enrolled during a median site-specific enrollment period of 12 months. The appropriate institutional review boards approved the study, and all participants provided written informed consent.

EWI data abstraction

Definitions of the selected EWI followed WHO/HIVResNet guidance [4] and are summarized in table 1. Data on PASER-M participants initiating first-line ART were used to abstract the following EWIs: ART prescribing practices, patients lost to follow-up (LTFU) at 12 months, patient retention of first-line ART, and viral load (VL) suppression at 12 months. The indicators "on-time ARV drug pickups" and "ARV drug supply continuity" were retrospectively collected from medical and/or pharmacy records. Indicator 4a (on-time ARV drug pickups) was modified from the WHO indicator and assessed for whether

Table 1. Definition of selected Early Warning Indicators

Indicator	Definition
1. ART prescribing practices	Percentage of patients initiating ART at the site who are prescribed, or pick up from the pharmacy, an appropriate[a] first-line ART regimen.
2. Patients LTFU at 12 months	Percentage of patients initiating ART at the site who are LTFU[b] 12 months later.
3. Patient retention on first-line ART	Percentage of patients initiating ART at the site who are taking an appropriate[a] first-line regimen 12 months later, excluding those who transferred out.
4a. On-time ARV drug pick-ups	Percentage of patients picking up all prescribed ARV drugs on-time[c] for two consecutive drug pick-ups after initiation of ART.
4b. On-time ARV drug pick-ups for 12 months	Percentage of patients picking up all prescribed ARV drugs on-time[c] during the first 12 months of ART or until classified as dead, transferred out or stopped ART.
6. ARV drug-supply continuity	Percentage of months in a designated year in which there were no ARV drug stock-outs.
8. VL suppression at 12 months	Percentage of patients initiating ART at the site with VL <1000 copies/ml after 12 months of first-line ART, excluding those who died or transferred out.

[a] An appropriate first-line ART regimen meets one or both of the following definitions: standard regimen listed in national ART guidelines and used according to those guidelines; regimen recommended in the WHO treatment guidelines. [b] Lost to follow-up is defined as a patient who has not returned to the clinic ≤90 days after the last missed appointment or drug pick-up during the first 12 months of ART, and who was not known to have transferred out, stopped therapy without restarting, or died. [c] On or before the date the previously dispensed drugs would have run out if taken according to schedule. Table adapted from WHO HIVDR early warning indicators guidance document; ART, antiretroviral therapy; ARV, antiretroviral; VL, viral load.

patients were on time for 2 consecutive drug pickups after initiation of ART; those who had been on ART for longer periods of time were not considered.

Medication possession ratio

The MPR was assessed using pharmacy pickup information during the first 12 months of ART for all patients with the exception of those who died or transferred out. The MPR was calculated by dividing the number of days a patient was in possession of ARVs by the 365 days in the first calendar year of ART [15].

Laboratory methods

HIV RNA testing for the survey was performed on EDTA anticoagulated plasma using the NucliSens EasyQ real-time assay version 2.0 (bioMérieux, Lyon, France) or the COBAS Ampliprep/COBAS TaqMan assay (Roche, Branchburg, New Jersey) at 2 reference laboratories in South Africa and Uganda.

Classification of virological outcomes

Viral load suppression, or HIVDR prevention, was defined as HIV RNA ≤1000 copies/mL after 12 months of first-line ART [20]. The outcome "possible HIVDR" applied to patients with HIV RNA > 1000 copies/mL after 12 months but also to patients who were LTFU, who were no longer on appropriate first-line regimens (due to stopping or switching ART), or from whom no follow-up specimen was available. Patients who transferred out or died in the first year of ART were censored from analysis because these outcomes are unlikely to be the result of HIVDR [20].

Statistical Analysis

World Health Organization data abstraction tools [4] were used to capture and calculate on-time ARV drug pickups. The sensitivity, specificity, positive and negative predictive values of the EWI "on-time ARV drug pickup" and the MPR for the identification of virological outcomes (VL suppression or possible HIVDR) were calculated with 95% confidence intervals (CIs) using 2 x 2 tables. The positive and negative likelihood ratios were derived from the sensitivity and specificity. All analyses were performed using Stata software version 10 (StataCorp, College Station, Texas).

RESULTS

Study sites and population

During the recruitment period from March 2007 to September 2009, 2735 patients initiated first-line ART. Less than 5% of patients reported any previous ARV exposure (i.e.,

Table 2. Early Warning Indicators results by site

	ART prescribing practices	Patients LTFU at 12 months	Patient retention on first-line ART	On-time ARV drug pick-ups	Drug-supply continuity[a]	VL suppression at 12 months[b]
WHO target	100%	≤ 20%	≥ 70%	≥ 90%	100%	≥ 70%
Site 1	116/116 (100%)	13/116 (11.2%)	81/115 (70.4%)	-	12/12 (100%)	70/96 (72.9%)
Site 2	228/228 (100%)	10/228 (4.4%)	192/223 (86.1%)	178/228 (78.1%)	12/12 (100%)	173/206 (84.0%)
Site 3	239/239 (100%)	31/239 (13.0%)	165/227 (72.7%)	156/235[c] (66.4%)	12/12 (100%)	147/200 (73.5%)
Site 4	205/205 (100%)	20/205 (9.8%)	156/199 (78.4%)	-	na[d]	139/185 (75.1%)
Site 5	204/204 (100%)	22/204 (10.8%)	162/193 (83.9%)	-	12/12 (100%)	132/185 (71.4%)
Site 6	223/223 (100%)	34/223 (15.3%)	177/220 (80.5%)	-	12/12 (100%)	154/214 (72.0%)
Site 7	203/203 (100%)	18/203 (8.9%)	174/202 (86.1%)	-	11/12 (91.7%)	140/193 (72.5%)
Site 8	215/215 (100%)	22/215 (10.2%)	176/215 (81.9%)	-	11/12 (91.7%)	156/200 (78.0%)
Site 9	221/223 (99.1%)	17/223 (7.6%)	173/222 (77.9%)	-	9/12 (75%)	159/192 (82.8%)
Site 10	220/220 (100%)	15/220 (6.8%)	184/213 (86.4%)	-	12/12 (100%)	152/199 (78.6%)
Site 11	223/223 (100%)	15/223 (6.7%)	200/217 (92.2%)	-	12/12 (100%)	169/215 (78.6%)
Site 12	229/230 (99.6%)	7/230 (3.0%)	211/230 (91.7%)	-	12/12 (100%)	186/223 (83.4%)
Site 13	206/206 (100%)	44/206 (21.4%)	148/205 (72.2%)	-	12/12 (100%)	127/199 (63.8%)
On target	11/13 (84.6%)	12/13 (92.3%)	13/13 (100%)	0/2 (0%)	9/12 (75%)	12/13 (92.3%)

[a] ARV drug supply continuity during the first year of the PASER-M survey. [b] Viral load as measured retrospectively for the PASER-M survey. [c] Patients who transferred out or died before the first pick-up were excluded from analysis. [d] No site dispensary. ART, antiretroviral therapy; ARV, antiretroviral; VL, viral load; NA, not applicable; WHO, world health organization.

for prevention of mother to child transmission, mono/dual therapy and/or ART) [19]. As shown in table 2, it was feasible to monitor 5 of the selected indicators at all sites. The EWI "on-time ARV drug pickups" was monitored at 2 sites. All patients at 11 of 13 (84.6%) sites were prescribed an initial first-line regimen according to WHO guidelines [21]. At site 9, 2 patients received first-line protease inhibitor (PI)–based regimens, and at site 12, an inappropriate triple-nucleoside reverse transcriptase inhibitor (NRTI) combination was prescribed.

Twelve (92.3%) sites met the targets of ≤20% patients LTFU, and all sites retained ≥70% patients on first-line ART after 12 months. The overall proportion of patients LTFU within the first year of ART was 9.8% across sites (range, 3.0%–21.4%). Inappropriate switch to PI-based or inappropriate substitution to triple-NRTI regimens within the first 12 months took place in 19 patients at 7 sites. A total of 19 patients at 8 sites were switched to second-line ART after suspected treatment failure.

Neither of the sites at which ARV drug pickups were monitored met the target for this indicator: 78% of patients at site 2 and 66% of patients at site 3 were on time for 2 consecutive pickups. When assessing pickups for the entire first year of ART, 4% of patients at site 2 and 6% of patients at site 3 were always on time (data not shown). Calculation of the MPR revealed that 86% of patients at site 2 and 59% of patients at site 3 were in possession of ARVs 100% of the time in the first year of ART. Antiretroviral drug supply was uninterrupted at 75% of sites. Three sites reported stockouts of fixed-dose combinations (FDCs), but not of individual ARV components, for a period of 1–3 months.

All but 1 site (92.3%) met the target of ≥70% of patients achieving VL suppression after 12 months of first-line ART. Overall, 76.0% of all patients in the cohort were classified as having VL suppression or HIVDR prevention. The remaining patients either had a VL >.1000 copies/mL (n = 166), had no available VL result (n = 148), were no longer on first-line ART (switch, n = 19; stop, n = 2), or were LTFU (n = 268) and were classified as having possible HIVDR.

Evaluation of adherence measures

As summarized in table 3, the indicator "on-time ARV drug pickup" had a sensitivity of 46.6% (95% CI, 35.9%–57.5%) and a specificity of 79.4% (95% CI, 74.6%–83.7%) for determining possible HIVDR after 12 months of first-line ART. An MPR of 100% yielded 67.0% (95% CI, 56.2%–76.7%) sensitivity and 83.5% (95% CI, 79.0%–87.4%) specificity. The positive predictive value of on-time ARV drug pickup and MPR were 38.3% (95% CI, 29.1%–48.2%) and 52.7% (95% CI, 43.0–62.2%), respectively. The positive likelihood ratios for the 2 measures were 1.6 and 3.9, respectively.

Table 3. Performance of on-time ARV drug pick-up and the medication possession ratio to determine possible HIV drug resistance[a] at 12 months

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR (%)	NLR (%)
On-time ARV drug pick-ups	46.6 (35.9-57.5) [41/88]	79.4 (74.6-83.7) [255/321]	38.3 (29.1-48.2) [41/107]	84.4 (79.8-88.3) [255/302]	1.6	0.8
100% MPR	67.0 (56.2-76.7) [59/88]	83.5 (79.0-87.4) [268/321]	52.7 (43.0-62.2) [59/112]	90.2 (86.3-93.4) [268/297]	3.9	0.4

Numbers in parentheses refer to the 95% confidence interval. Numbers in square brackets refer to the numerator and denominator from which the relevant percentages are calculated. Medication possession ratio is defined as the amount of time an individual is in possession of ARVs divided by the time between ARV prescriptions. [a] Possible HIVDR defined as patients with viral load > 1000 c/ml, patients lost to follow-up, patients who were no longer on appropriate first-line regimens (due to stopping or switching ART), or from whom no follow-up specimen was available. ARV, antiretroviral; MPR, medication possession ratio; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

DISCUSSION

The assessment of the WHO-recommended EWIs as part of the ongoing PASER-M study at 13 public and nongovernmental ART sites in 6 African countries has identified vulnerable aspects of ART program functioning that are potentially associated with the emergence of HIVDR. Feedback to the respective sites is expected to trigger interventions targeted at the most at-risk populations. The measurement of the MPR, as a proxy measure for drug adherence, appeared to have better performance to predict possible HIVDR after 12 months of ART than the indicator "on-time ARV drug pickups."

Monitoring the indicator "on-time ARV drug pickups" was not feasible at all sites because patient or pharmacy records were found to be incomplete or could not be easily accessed even though the required data may have been routinely collected. The complexity associated with extracting the data required for the drug pickup indicator has been reported previously [5, 6]. The percentage of patients picking up ARVs on time for the entire first year of ART was unrealistically low, suggesting that this indicator may be too stringent or potentially signaling that pharmacy data may be unreliable. Notably, the indicator assessing 2 consecutive drug pickups after ART initiation achieved better performance in predicting virological outcomes. With a specificity of 79.4%, this cross-sectional indicator may be useful in correctly classifying persons in whom VL suppression will be achieved and could serve as a practical tool for clinics: adherence should be strongly reinforced in patients who fail to refill 2 drug pickups on time. Significantly, the MPR yielded higher sensitivity, specificity, and positive and negative predictive values than did ARV pickup information. As reflected by the positive likelihood ratio, patients with an MPR <100% were 3.9 times as likely to be classified as having possible HIVDR after 12 months of ART compared with patients with perfect medication possession. The MPR was therefore more accurate in identifying patients at risk of HIVDR development than pickup information alone, which had a positive likelihood ratio of 1.6.

The assessment of ART prescribing practices is relevant as inappropriate drug combinations have been documented to lead to the development of HIVDR [22]. The rate of correct prescribing was high, but did not reach 100% at all sites. One patient received an inappropriate triple-NRTI regimen for unknown reasons. Protease inhibitor–based first-line regimens were prescribed for 2 patients diagnosed with Kaposi sarcoma at site 9, in spite of the recommendation to reserve these drugs for second-line therapy in the setting of limited formularies [21].

Limiting attrition is essential because returning patients who were previously LTFU risk virological failure due to selected drug-resistant virus [23]. The attrition rate was lower

than has previously been reported in African ART programs [24] but varied substantially between sites. The site with the highest proportion of patients LTFU (21.4%) serves an urban, mobile population and performs limited patient tracing. Failure to correctly classify patients as deceased might have contributed to a high proportion presumed LTFU at both clinics that did not meet the indicator target. This underscores the importance of proper administration at ART sites for obtaining reliable EWI results. All sites met the target for patient retention on first-line ART at 12 months, which highlights the general effectiveness of first-line regimens and the success of managing toxicity with in-class substitutions. For 15 patients at 7 sites, inappropriate substitutions within first-line regimens to PI-based regimens occurred, limiting durable second-line options.

Because treatment interruptions may lead to HIVDR in resource-limited settings [25], it is essential that ARV drug supply continuity be monitored strictly. The sites that did not meet the indicator target had stockouts of FDCs that were replaced by the individual ARV components. Even though FDC stockouts lasted up to 3 months (site 9), they did not result in stopping or changing of individual patients' regimens.

Lastly, the optional indicator "VL suppression at 12 months" identified 1 clinic in which <70% of patients achieved HIVDR prevention. This poor performance was largely due to the high rate of patients LTFU at this clinic. Patient retention and tracing are the most important programmatic factors to be targeted for improvement at this site, which failed to meet 2 of 5 EWI targets.

The current study has some limitations. Because the PASER-M study used eligibility criteria, the population may not be completely representative of the general clinic population. However, additional selection bias is likely to be limited because all new patients who qualified for ART initiation were screened and enrolled in the study consecutively within a limited median time period of 12 months [19].

In conclusion, this pilot assessment of EWIs in the PASER clinical network has identified deficiencies in ART site functioning that should be targeted to minimize the emergence of preventable HIVDR. Nine sites failed to meet at least 1 EWI target; this should raise concern and flag those aspects of the clinic or pharmacy that need to be improved. This report provides the first example of how the WHO site-based EWIs, part of the WHO global strategy for HIVDR prevention and assessment, have been successfully abstracted and evaluated within an ongoing population-based monitoring study. Early warning indicators approximating drug adherence appeared to be helpful in identifying patients at risk for the development of HIVDR who would benefit from targeted adherence support. Based on our findings, the assessment of on-time refilling for 2 consecutive drug

pickups as opposed to the entire first year of ART was more feasible and informative. Our data suggest an additional advantage of the MPR over pickup information, because this measure was better able to predict possible HIVDR emergence. Further studies should focus on examining the MPR target or threshold necessary to prevent treatment failure and HIVDR. Based on its feasibility and performance, it is recommended to incorporate MPR in future EWI monitoring efforts to estimate patient adherence to ART. In addition to the ongoing laboratory-based studies to assess transmitted and acquired HIVDR within the PASER network, EWI monitoring will contribute to improved ART site functioning and quality of care for HIV-infected persons in sub-Saharan African countries.

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